RON BUTLER'S RANGE OF SCIENTIFIC INQUIRY

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INTRODUCTION

Dr. W. R. (Ron) Butler began his career studying testicular function in the rat in the late 1960's. From that time, he has traversed from the hypothalamus to the ovary to the uterus in a diverse array of species. His work has covered the span from basic to applied studies. Regardless of the species or reproductive organ studied, a recurrent theme in his work is the timeliness and importance of the question asked. This has led to a career of "firsts" where important findings arose from hypothesis-driven research. Ron Butler has trained under, collaborated with, and trained some of the best-known animal reproductive biologists of his era. His resume includes over 100 refereed journal publications with over 8000 citations. His h-index (Scopus) is an impressive 45.

EARLY YEARS

Ron began his academic career at Ohio State working with W. R. "Reg" Gomes on testicular function in the rat (Butler et al., 1968). He later moved to Purdue University training under Dr. Paul Malven and collaborating with Dr. Doug Bolt from USDA Beltsville. It appears that his love for luteinizing hormone (LH) began at Purdue with the studies of pituitary LH release in the ovariectomized ewe (Butler et al., 1972). This work, published in the journal *Endocrinology* not only included detailed profiles of LH but also included the development and validation of a radioimmunoassay for ovine prolactin. Radioimmunoassay was a new technology at the time and the development of the prolactin assay to replace cumbersome bioassays was an important scientific achievement. Following the completion of his work at Purdue, Ron moved to the laboratory of Ernst Knobil; one of the most iconic scientists in all of reproductive biology and a graduate of Cornell Animal Science. Knobil was Chairman of the Department of Physiology at the University of Pittsburgh School of Medicine where he studied the regulation of the menstrual cycle in rhesus monkeys. The classic work from the Knobil laboratory created the basis for much of our understanding of how LH controls reproductive cycles in mammals. To this day, reproductive biology students are taught the "Knobil model" for LH control that includes elements of Ron's work. Fellow lab mates from this era included Fred Karsch who later moved to an illustrious career at the University of Michigan where he continued to work on LH secretion and developed surgical procedures for cannulation of the portal vein in sheep. Ron was an NIH fellow within the Knobil laboratory and published 15 papers with Knobil. His publication record with Knobil was second only to that of Rob Gilbert of the College of Veterinary Medicine at Cornell (co-author of 16 publications). His two first-author publications in *Endocrinology* included work on the control of thyroxin secretion (Butler et al., 1975b) and work on the luteolytic mechanisms in the rhesus monkey (Butler et al., 1975a).

GETTING STARTED AT CORNELL

Ron moved to Cornell in 1975 and immediately established his endocrine laboratory. Early collaborations were with Bill Hansel from the Department of Physiology of Cornell where they studied the endocrinology of dogs (Concannon et al., 1978). Ron's first publication in the *Journal of Dairy Science* was a description of a radioimmunoassay that could be used to measure cortisol in milk (Butler and Des Bordes, 1980). He followed this work with several studies in which milk cortisol was examined as a possible indicator of stress in dairy cows (Fox et al., 1981; Termeulen et al., 1981).

Ron's work in the Knobil laboratory studying the reproductive cycles of monkeys clearly stimulated an interest in understanding the mechanisms that control the interval to first ovulation in dairy cows. Cows that fail to ovulate postpartum are infertile. First ovulation, therefore, was then and continues to be a keen interest of reproductive biologists. His earliest publication on this topic was a collaboration with Cornell dairy geneticist Bob Everett and fellow Cornelian C. E. Coppock (Butler et al., 1981a). The abstract of this paper concluded, "energy balance during the first 20 days of lactation is important in determining the onset of ovarian activity following parturition". Also included in this publication was the idea that first ovulation occurred approximately 10 days after the nadir in energy balance. These two concepts that energy balance controlled the interval to first ovulation in dairy cows and that the first ovulation occurs 10 days after the energy balance nadir are widely held to this day. Authors have cited this paper over 225 times.

THE 1980'S

The 1980's was a period of intense scientific discovery within the Animal Science Department at Cornell. Ron's laboratory turned to puberty and seasonality in the ewe and investigated the effects of photoperiod, nutrition, and ram exposure (Butler et al., 1981b, 1987; Fitzgerald and Butler, 1982, 1988; Fitzgerald et al., 1982). In addition to these studies, he collaborated with those working actively on animal growth including Dr. Dean Boyd working with pigs (Boyd et al., 1985) and Dr. Don Beerman working with cimaterol in sheep (Beerman et al., 1987; O'Connor et al., 1991b; a). His work in reproductive biology included three studies in swine in which ovulation rate, pregnancy, and the use of relaxin to synchronize farrowing were studied (Butler and Boyd, 1983; Pope et al., 1986; Fu et al., 1990). Ron's colleague, Dean Boyd, considers the work on relaxin to have had a major impact on modern farrowing management in the swine industry. Ron also completed studies on the control of gonadotropin secretion with fellow Cornell reproductive biologist Bob Foote (Butler et al., 1983).

BACK TO LH

It was the mid to late 1980's when Ron returned to the topic of energy balance and postpartum cyclicity in dairy cows with graduate student Rick Canfield. Their work during this period clearly established the model for LH pulsatility and the resumption of

postpartum reproductive function in dairy cows that continues to be used today (Canfield and Butler, 1990, 1991). It was at about this time that Ron published his most highly cited paper “Interrelationships between energy balance and postpartum reproductive function in dairy cattle” with fellow Cornelian R. D. Smith (Butler and Smith, 1989). This paper documented the steady decline of reproductive performance of dairy cattle over time and detailed physiological mechanism that could potentially explain the decline. This paper was the first in a series of highly cited review papers authored by Ron on energy balance and reproductive function in dairy cows (Butler and Smith, 1989; Beam and Butler, 1999; Butler, 2000). Collectively, authors have cited these review papers nearly 1500 times.

PROTEIN NUTRITION AND FERTILITY

In addition to their work on LH, Canfield and Butler published groundbreaking work on protein nutrition and fertility with Cornell dairy nutritionist Charlie Sniffen (Canfield et al., 1990). At the time, farmers were overfeeding protein to maximize milk production. Canfield reported that feeding a 19% compared with 16% crude protein in the diet increased plasma urea concentrations and reduced first service conception rate by 17 percentage points. Canfield’s initial work was followed soon thereafter by graduate student Charlie Elrod working in Butler’s laboratory. Elrod was able to show that overfeeding soluble protein and increasing plasma urea caused a decrease in uterine pH (Elrod and Butler, 1993; Elrod et al., 1993) that is apparently detrimental to the embryo. Elrod’s work was followed by a field trial conducted by Butler and graduate student Steve Beam showing a 20-percentage point reduction in conception rate for cows with a plasma or milk urea concentration of greater than 19 mg/dL (Butler et al., 1996). The collective work from his laboratory led to one of the most highly-cited review papers on protein nutrition and reproduction in the *Journal of Dairy Science* entitled “Effect of protein nutrition on ovarian and uterine physiology in dairy cattle” (Butler, 1998) (302 citations). In later work, Butler graduate student Michelle Rhoads performed mechanistic work and showed urea infusion would decrease uterine pH compared with a saline-infused control (Rhoads et al., 2004). Furthermore, she demonstrated that elevated plasma urea nitrogen decreased the viability of the early embryo (Rhoads et al., 2006).

INSULIN-LIKE GROWTH FACTORS COME INTO FOCUS

The groundbreaking work from the Butler lab clearly implicated LH pulsatility as a major driver of postpartum ovulation of the dairy cow. It became clear, however, that the concentration of systemic growth factors could modulate the LH response. One of the best studied of these was insulin-like growth factor I (IGF1); a major hormonal product of the liver that was known to respond to the energy balance of the cow. Butler teamed up with Cornell graduate student Steve Beam in a series of studies to establish the link between energy balance, circulating IGF1, and ovarian follicular growth measured by ultrasound. Their first paper published in the *Biology of Reproduction* established the important concept that there are three fates of the first wave dominant follicle postpartum; namely ovulation, failed ovulation (turnover) or cyst formation (Beam and

Butler, 1997). These fates were tied to circulating estradiol concentration (arising from the follicle) and circulating IGF1 (favorable outcomes associated with greater IGF1 in the circulation). The important link between energy balance, IGF1, follicular function and ovulation early postpartum was further explored and confirmed in a second paper published in the *Journal of Dairy Science* (Beam and Butler, 1998). Their collective work was presented at the prestigious Fifth International Symposium on Reproduction in Domestic Ruminants held in Colorado Springs Colorado in August 1998. The review paper that arose from that presentation presented a clear model for how IGF1 and LH work collectively to increase circulating estradiol and trigger the LH surge leading to first ovulation (Beam and Butler, 1999). The working model is widely accepted today. The paper is Ron's third most-highly cited publication (343 citations).

LINKING INSULIN TO IGF1

The systemic IGF1 that Beam and Butler studied arises primarily from the liver and is under metabolic control arising from the nutrition and energy balance of the cow. The somatotropic axis is "uncoupled" for cows in negative energy balance. The mechanism underlying the uncoupling was an important question of the time. Postpartum cows have low circulating glucose and insulin concentrations. Ron explored this question with graduate student Stephen Butler. In a landmark study, Butler demonstrated that insulin infusion recoupled the somatotropic axis and increased IGF1 through a mechanism that involved growth hormone receptor (GHR) 1A (Butler et al., 2003). Stephen Butler went further to demonstrate that positive effects of insulin and IGF1 on the follicle could occur independent from changes in LH pulse frequency (Butler et al., 2004). Butler later went on to test propylene glycol drench as a practical method to improve hormonal and metabolic status and stimulate follicular development postpartum (Butler et al., 2006). Although the treatment failed to improve reproductive outcomes, the publication reestablished the importance of negative energy balance and introduced the relatively new concept that the low dry matter intake and energy balance in non-ovulatory cows could be detected *before* calving. This study was one of the first that linked postpartum reproduction to the metabolic profile of the dry cow.

PRACTICAL SOLUTIONS FOR THE POSTPARTUM COW

Ron always had an interest in solving problems that face dairy producers. His laboratory published a series of papers that examined the utility of feeding different formulations of fat including protected fats (Beam and Butler, 1997, 1998) and fish oils (Moussavi et al., 2007a; b). He collaborated with Dale Bauman's lab in their work on conjugated linoleic acid (CLA) (Chouinard et al., 2001; Castañeda-Gutiérrez et al., 2005, 2007; Corl et al., 2006). Collaborating with Michael De Veth, Butler demonstrated that feeding CLA early postpartum could improve reproductive outcomes (de Veth et al., 2009). The potential to use CLA to improve postpartum reproduction was confirmed in subsequent studies (Csillik et al., 2017).

In addition to feeding, Butler explored practical ways to increase progesterone and stimulate cyclicity in postpartum cows. This included work in postpartum cows (Larson et al., 2007). Butler's lab also participated in the original trials that let to FDA approval or progesterone-releasing CIDR devices that are widely used today (Lucy et al., 2001). In one of Ron's last collaborations with Dr. William Hansen before Hansel's retirement from Cornell, Rod worked on a process called "inembryonation" where estrus was synchronized using a CIDR device and $PGF_{2\alpha}$ and a "one-step" frozen embryo was transferred on day 7.

LATER YEARS

During the later years of his career, Ron continued his research with his long-time collaborator Yves Boisclair from the Cornell Department of Animal Science. Yves and Ron shared an interest in metabolism and potential effects on fertility in the dairy cow. Several important concepts arose from their work on the adipose tissue hormone leptin. They showed that 1) leptin decreased in response to negative energy balance (Block et al., 2001); 2) hypoinsulinemia postpartum caused an increase in leptin receptor in liver (Thorn et al., 2008) and; 3) leptin is an important signal leading to the conservation of glucose in early postpartum cows (Ehrhardt et al., 2016). Their latest work includes one of the few publications on adiponectin in dairy cows (Krumm et al., 2017).

Ron co-published more papers with Rob Gilbert (Cornell University College of Veterinary Medicine) than any other author. Ron and Rob's final period of collaborative work focused on uterine disease and its effect on fertility in the postpartum cow as well as basic biology of the ovarian follicle postpartum (Galvão et al., 2009, 2010; Vieira-Neto et al., 2014; Cheong et al., 2016, 2017). The lead authors on their collaborative publications included two Ph.D. students who are now highly regarded faculty members in Colleges of Veterinary Medicine (Klibs Galvão now at the University of Florida and Soon Hon Cheong at Cornell).

SUMMARY

Ron Butler's career spanned several decades and contributed greatly to the field of animal reproductive biology. His career embodied that of a creative and productive faculty member who remained active and relevant from early to later years. He collaborated with many individuals both within and outside the Department of Animal Science at Cornell. He trained many great scientists who work in both industry and academia. Their work will continue his scientific legacy into the future. Not included in these pages is a list of the many students who benefited from Ron's knowledge both inside and outside the classroom. These students may not have completed and published research projects under his guidance but nonetheless benefited from his knowledge and inspiration.

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